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Human Genetic Factors as Determinants of Resistance to Malaria: A systematic Review

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Abstract: Introduction: Malaria is one of the strongest known forces of evolutionary selection in the recent history of the human genome, having had important implications in human adaptation and in the response to its infections. The objective of this systematic review was to provide an update on human genetics that have been described as affecting the human susceptibility to malaria around the world and particularly in Africa. **Methods**: Through world wide web research vectors and using PubMed and Google Scholar, we reviewed relevant original articles, review papers, short reports, and peer-reviewed papers on human genetics factors described as related to human susceptibility to malaria. Here, we reviewed the literature on human genetic polymorphisms associated with protection from *Plasmodium* infections and/or disease. **Results**: After reviewing and summarizing 140 manuscripts, we found that several factors appeared to hamper an effective control of malaria, including the complex biology of *Plasmodium* parasites, parasite genetic diversity, environmental factors, resistance to antimalarial drugs, and the lack of a highly effective vaccine for public health use. Although the cellular and molecular regulatory mechanisms underlying the pathogenesis of disease are still not fully understood, it is well-established that genetic determinants of the host play an important role in the outcome of infection and the severity of the disease. **Conclusions**: The interaction between malaria parasites and humans has led to the selection of several inherited traits conferring protection against malaria, such as hemoglobinopathies, enzymopathies, and immunogenetic variation, whilst others polymorphism describes susceptibility to the infection.

Keywords: genetic factors; resistance; selection; adaptation; malaria

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1. Introduction

Although there has been a sharp decrease in malaria incidence and deaths over the past seven years, malaria remains a major public health concern. The World Malaria Report of 2021 estimates that there were 241 million malaria cases in 2020 in 85 malaria-endemic countries [1]. More than 10% of children in low-income countries, compared to less than 1% in high-income countries, die before the age of five, primarily due to infectious diseases such as malaria, respiratory infections and diarrhea [2]. The high level of genetic diversity of malaria parasites in the African continent has been shown to hamper elimination strategies and sustains the high burden of the disease [3]. During its co-evolution with malaria parasites, the human genome developed adaptive mechanisms of survival driving to phenotypic diversity. All of these phenomena contribute to the complexity of malaria susceptibility. Therefore, a deep understanding of human genome diversity, the mechanism of gene flow and adaptive processes may help develop and refine elimination strategies.

Malaria is an infectious disease transmitted to humans mainly by infested mosquitoes. Following its introduction into the human body, the malaria parasite will undergo replication in the liver before being released into the blood stream. Throughout its life cycle, the parasite is exposed to the host immune system, which is developed to contain the progress of the parasite life cycle. As a result, the parasite evolves mechanisms to evade host immune responses through redundant invasion mechanisms and extensive genetic diversity in parasite surface antigens. All of these mechanisms are sustained by specific genes; therefore, any change in gene sequence may result in changes in the parasite evasion mechanism. Researchers believe that this ability makes the parasite more adaptable when attempting to invade human cells. These functional mechanisms and recent findings suggest that malaria outcome is influenced by diverse factors including environmental, parasite, and host factors, e.g., genetics, nutrition, age, and immune status [4]. Biologically, the invasion phase of red blood cell initiates a complex immune response involving cooperation between B-cells, T-cells and antigen-presenting cells [5].

Malaria, the strongest evolutionary selective force in the recent history of the human genome [6], leads to human adaptations that comprise some of the most common Mendelian diseases of mankind [7]. These adaptative traits have evolved independently in different malaria-endemic populations [8,9], such as hemoglobin S (*HbS) and Hemoglobin C (HbC)*, which have risen to a high frequency despite the fatal consequences for homozygote carriers [8].

In this review, we aim to outline host genetic factors that may influence human resistance and susceptibility to malaria in order to demonstrate how the co-evolution of the malaria parasite and the human host has led to the selection of human genetic factors and how these genetic changes have been shown to limit malaria disease and mortality [8,10–13].

2. Methods

Through world wide web research vectors and using PubMed and Google Scholar, we reviewed relevant original articles, review papers, short reports, and peer-reviewed papers on humans. We systematically reviewed all of the relevant available articles, manuscripts and other review papers that described the impact of the co-evolution between Homo Sapiens and plasmodium on the human genome. The keys words were Hemoglobinopathies and Malaria, G6PD and Malaria, Evolution of malaria parasite and human genome, Duffy blood group antigens and Malaria, ABO blood group and Malaria, Glycophorins and malaria, and Immunogenetic factors and Malaria. We included all articles that are related to human genetic determinants and susceptibility or resistance to malaria. After removing duplicates, original articles, manuscripts, and short reviews that described hemoglobinopathies and malaria, erythrocyte surface antigens and malaria, enzymopathies, and malaria and immunogenetic factors related to protection against malaria were selected, read and summarized on this review paper.

3. Results and Discussion

We reviewed a total of 140 original articles, review papers, systematic reviews, and short communications. The results show that recent genomic and genetic studies have provided evidence that human adaptations play an important role in determining the outcome of initial infection for many pathogens [14–16], including malaria [17]. While genome-based protection of humans from malaria was attributed to additive genetic effects, only a small proportion was attributable to well-known genetic factors [18], such as sickle-cell trait. The genetic basis of host resistance or susceptibility to malaria is complex and polygenic, and has evolved over millennia as a result of interactions between the human host, the parasite, and the environment [8]. Epidemiological data indicated that human genetic factors explain approximately 25% of the malaria risk in Africa [19]. The first studies of human genetic determinants of susceptibility to clinical malaria were conducted in the 1950s [20]. Since then, genomic approaches and genome-wide association analyses have identified new genetic regions potentially contributing to host resistance to malaria [18,19]. While many human genetics polymorphisms have been reported to be associated with resistance to malaria, few have been reliably replicated [21]. A refined approach to host genetic susceptibility or resistance to malaria would be fundamental for understanding host parasite interactions and may aid in the identification of new therapeutic targets that leverage these naturally acquired host resistance mechanisms.

3.1. Hemoglobinopathies

Hemoglobin polymorphism was described as the first host genetic factors identified to contribute to human risk to malaria [22], and, nowadays, several text books provide examples of heterozygote advantages of evolutionary biology [22]. While sickle-cell trait is the most well-known hemoglobinopathy [23], other hemoglobin polymorphisms have also emerged in endemic areas and contribute to host resistance to malaria. Normal hemoglobin is known to have no impact on malaria susceptibility. However, abnormal hemoglobin derived from mutations on the globin gene, on modifications of nucleotides numbers, mispairing or crossover during meiosis, have been shown to be related to susceptibility to malaria [24].

3.1.1. Hemoglobin S

Hemoglobin S (HbS) is the type of hemoglobin resulting from a mutation at position 6 of the β-globin chain ($\beta^{6\text{Glu-Val}}$). Although the homozygosity for hemoglobin S *(HbSS)* is associated with sickle-cell anemia, individuals with the heterozygous variant for *HbS (HbAS),* especially young children, are protected against severe malaria [25]. The mechanism through which the mutation provides protection from severe malaria is still under investigation. However, the impairment of cytoadherence by *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1), a parasite major cytoadherence ligand and virulence factor, with parasitized AS and SS erythrocytes may play a role in reducing symptomatic and severe malaria [26].

HbS homozygosity (SS) leads to sickle-cell disease, which is debilitating and often fatal. The disease is caused by red cell deformities that result from a structural defect, particularly at low oxygen concentrations.

Genetically, the protein of hemoglobin is encoded by the β-globin gene (HBB gene) located on chromosome-11 of human genome [27]. Even heterozygotes (AS), in which the A allele indicates the non-mutant form of the β-globin gene, provide resistance to malaria [18]. It is universally accepted that sickle-cell disease, which is caused by a single mutant gene, is responsible for the production of different types of hemoglobin in several aspects from a normal hemoglobin [23,28]. Earlier studies showed that more than 20% of Africans have the trait [29]. It is thought that malaria parasite growth is suppressed in heterozygote AS individuals [18]. In 2001, a clear association was established between sickle-cell anemia and reduced susceptibility to malaria [16,30]. Moreover, the prevalence of the HbS

allele in malaria-endemic regions was shown to result from natural selection [16]. Haplotype analysis of the pattern of single nucleotide polymorphisms (SNPs) in the β-globin gene cluster determined that the HbS allele emerged at least twice, once in Africa and once in India or in the Middle East [31]. The SNP responsible for HbS, rs334, was present at all African study sites, with heterozygote frequencies in controls ranging from 0.05 (Malawi) to 0.22 (Nigeria) [21].

3.1.2. Hemoglobin C

Hemoglobin C (HbC) is a different structural variant of hemoglobin caused by an amino acid substitution of lysine for glutamic acid at position six on the beta hemoglobin chain. The version is equally encoded by the same region of the *HBB* gene found in several parts of West Africa, although it is less common than HbS [32]. Homozygote individuals for HbC (HbCC) have a significant reduced risk of malaria compared to normal HbAA [33]. A recent study indicated a diminished cytoadherence of parasitized HbC erythrocytes as a mechanism of protection to malaria [34]. Heterozygotes (HbAC) display more moderate protection against malaria and do not experience a significant reduction in hemoglobin level, as demonstrated by Diallo et al. in Mali in 2004 [35]. Hemoglobin C (HbC) is a host polymorphism resulting from an SNP at *rs33930165.* The geographic distribution of HbC is considerably more limited than that of HbS, being centered on West and North-West Africa, with the exception of a low-frequency corridor between West Africa and Egypt that appears to reflect the patterns of human migration [36]. The prevalence of HbC varies by region in most West African countries, while both HbS and HbC alleles co-circulate in the same populations [37]. However, in Northern Ghana, the incidence of HbC heterozygotes (29%) was inversely proportional to the frequency of sickle-cell trait [38].

The association between HbC and malaria susceptibility is found to be controversial. In fact, a study conducted in Mali found that the incidence of clinical malaria was higher in HbAC children compared to children carrying the HbAA trait [39], whereas in Burkina Faso, *HbC* has been associated with a reduction in risk of clinical malaria [40]. Moreover, still in Burkina-Faso, a family-based association study including 53 families living in an urban area revealed a negative association between hemoglobin C levels and mild malaria episodes [41]. Several other studies have demonstrated the protective effects of hemoglobin C trait against severe malaria among the Dogon population in east-central Mali [11,40,42].

Early in vitro culture studies suggested a reduction in malaria parasite growth in HbC erythrocytes [40]. However, this potential protective mechanism has not been supported by in vivo studies [9]. New findings suggest that the expression of *P. falciparum* membrane protein-1 (PfEMP1), an important red-cell adhesion protein, is reduced in carriers of the HbC trait. A dose–response effect was observed, with the highest protection being detected in homozygotes [43]. More recently, Travassos et al. concluded that hemoglobin C trait protects against clinical malaria in Mali [44].

3.1.3. Hemoglobin E

Hemoglobin E (HbE) is another structural variant caused by a glutamic acid to lysine substitution at codon 26 [45] and encoded by the same HBB gene. This variant of hemoglobin appears to reduce erythrocyte invasion by merozoites, lower intra-erythrocytic parasite growth, and enhance the phagocytosis of infected erythrocytes [46,47]. In 2002, Chotivanich, K. et al. described that homozygous individuals for HbE have a mild thalassemia phenotype, whereas heterozygotes have no clinical or hematological manifestations [47]. Hemoglobin E (HbE) trait has been associated with protection against malaria [47]. Adults with HbE trait were found to have a reduced severity of disease in field studies [48]. However, more field studies are still needed to provide convincing evidence of the association between HbE and malaria susceptibility, as requested by other authors [25]. The severity of acute *P. falciparum* was ameliorated in the presence of HbE [49]. In sum, epidemiologic studies have repeatedly shown a positive association of HbEE or HbAE with reduced malaria cases.

However, the evidence is inconsistent and reported from different countries and regions. Available data are not sufficient to perform an aggregated analysis such as a standard meta-analysis and a meta-regression [49].

The rs33950507 SNP responsible for HbE is less frequent in the malaria-endemic regions compared to HbS and HbC and is most common in parts of Southeast Asia [50]. The distribution of HbE is primarily limited to the Emerald Triangle region where Thailand, Laos, and Cambodia share borders, although the frequency of HbE differs among local populations [51], and can reach carriage rates of 50% in some populations. Analyses of the evolution of the Southeast Asian HbE allele suggest that it originated within the past 5000 years [52].

3.1.4. Thalassemias

Another hemoglobin structural variant, the thalassemias, is a heterogeneous group of genetic disorders that result from the reduced or absent synthesis of the α- or β-globin chains in erythroid cells during hematopoiesis (α2β2) [53]. The thalassemias result from deletions and other disruptions of globin gene clusters on chromosome 11 and 16 [54]. Alpha-thalassemias originate from deletion and point mutations of genes encoding the alpha globin chains [55], while more than 200 mutations and rare deletions in the β-globin gene have been characterized as determinants of β-thalassemias [56].

Globally, the incidence of the thalassemia is high in a broad area extending from the Mediterranean basin and parts of Africa, throughout the Middle East, the Indian subcontinent, Southeast Asia, Melanesia and the Pacific Islands [57]. However, mild forms of α-thalassemia, which result from a single gene deletion (2a/aa), occur in a broad tropical belt stretching from sub-Saharan Africa through the Mediterranean and Middle East to the Indian subcontinent and the whole of East and Southeast Asia, while β-thalassemia is known to occur in localized parts of sub-Saharan Africa and sporadically throughout the Middle East and the Indian subcontinent [32].

The suggestion that thalassemias have been selected by malaria is based mainly on epidemiological studies. There is a significant altitude- and latitude-dependent correlation between the frequency of α-thalassemia and the endemicity of *Plasmodium falciparum* in the Southwest Pacific [58,59]. Direct evidence of protection of α^+ thalassemia trait against severe malaria, both in homozygote and heterozygote carriers, has been shown in a study conducted in Papua New Guinea [60]. Polymorphisms at specific loci on human chromosome [61] have also been associated with susceptibility to malaria infection [62,63]. Moreover, it has been found that complement receptor 1 (CR1) expression, which is required for rosette formation, is reduced on α^- thalassemic red cells, offering a possible mechanism for reduced rosetting [64]. Rosetting is definitively found to contribute to malaria pathology by causing microvascular obstruction and impaired tissue perfusion [64]. Infected α^- thalassemic red cells were shown to be less able to adhere to human endothelial cells [65,66]. The protective mechanism of thalassemias against malaria disease remains not fully understood [8]. However, it is thought to be multifactorial and related to the reduced expression of β -globin (HBB), α-globin2 (HBA2), or α-globin1 (HBA1) [67].

3.2. Erythrocyte Surface Protein Modifications

The surface of human red blood cell is covered by antigens that are receptors of parasite ligands during malaria infection. *P. falciparum* has an expanded family of erythrocyte binding ligands that target different sets of human receptors on the erythrocyte [68,69]. Mutations or modifications of these erythrocyte surface proteins may result in the disruption of ligand–receptor binding directly or by changing the surface tension or rigidity of the erythrocyte itself, all conferring resistance to *Plasmodium* infection. Here, we will focus on two main surface antigens: Duffy blood group antigens and ABO blood group antigens.

– **DUFFY BLOOD GROUP ANTIGENS.**

The Duffy Antigen Receptor for Chemokines (DARC), also known as Fy glycoprotein (FY) or CD234 (Cluster of Differentiation 234), is a protein that is encoded by the *DARC* gene [13,68]. The antigen is a multimeric red cell membrane protein organized into seven transmembrane domains and is a well-known erythrocyte receptor for *P. vivax* and *P. knowlesi* invasion. The DARC-encoding gene holds multiple allelesm including the codominant Fy^a and Fy^b, producing four primary genotypes: Fy(a+b+), Fy(a+b−), Fy(a−b+) and Fy(a−b−) [70], with the latter also being referred to as Fy-null [18]. The Fy-null genotype results in a lack of DARC expression on erythroid cells [71]. Red blood cells that lack the Duffy antigen have been shown to be resistant to invasion by *P vivax* [13], which is thought to have contributed to lower burden of *P. vivax* in some areas of sub-Saharan Africa [72]. The resistant phenotype in black African was describe to be associated with a point mutation at position T −33C [72], suggesting that *P. vivax* only infected Duffy-positive individuals. However, epidemiological studies, first in Africa [13] and later in Papua New Guinea [73], have revealed *P. vivax* infections in Duffy-negative populations, suggesting that there are DARC-independent mechanisms of *P. vivax* invasion [57]. Today, several researchers have reported malaria infection on Duffy-negative individuals, demonstrating the existence of an alternative path of transmission of *P. vivax* among Duffy-negative populations [74] to be investigated. A recent work on the transferrin receptor as an alternative pathway for *P. vivax* invasion demonstrated that invasion of immature red blood cells by the *Plasmodium vivax* is mediated by binding to the hosts transferrin receptor [75].

– **ABO BLOOD GROUP.**

Identified by Austrian immunologist Karl Landsteiner in 1901, the ABO blood group constitutes a series of antigens exhibiting similar serological and physiological characteristics and inherited according to a specific pattern [76]. The gene *ABO* encodes the glycosyltransferase enzyme, which determines the ABO blood group. Association between the ABO blood group and malaria susceptibility has long been suspected [77]. In fact, Cserti and Dzik suggested that there is substantial evidence supporting a protective effect of blood group O against malaria [78]. In three African populations, Fry et al. showed a strong association between type O blood and protection against severe malaria, and found that this effect was recessive [18], while Bayoumi et al. [77] and Igbeneghu et al. [79] observed no association between malaria prevalence and ABO blood types in central Soudan and Nigeria, respectively. Moreover, several other authors found a significant association between blood group and *P. falciparum* malaria in cross-sectional and case–control studies in Brazil, Gabon, India, Sri Lanka and Zimbabwe [80–84]. In fact, Cavalli hypothesized that the distribution of the major blood groups may reflect natural selection due to population exposure to infectious disease [85]. Blood group O was found to be less able to form rosettes in acute malarial infections and provide a protective effect in primigravid women in Ghana [86]. Elsewhere, evidence of a significant association between severe malaria and blood group A has also been observed [76]. Although the mechanisms for protection are not fully understood, the association between blood group A and severe malaria [54,83] is consistent with the low frequency of this blood group in many areas where malaria is endemic. It is possible that this effect is mediated by the modulation of rosetting, which has been observed in association with some strains of *P. falciparum* and different ABO (H) blood types in particular type O [78]. Genetically, a non-synonymous coding SNP, rs8176746, in ABO that is in linkage disequilibrium (LD) with the nucleotide deletion that determine type O has been associated, in a dominant gene model, with increased risk of severe malaria [21]. More recently, Julian Rayner et al. showed that the Dantu blood group confers resistance to severe malaria through a slight increase in red cell surface tension, which makes it difficult for *Plasmodium falciparum* to invade the cell [87].

– **GLYCOPHORINS**

The glycophorins constitute a group of red blood cell (RBC) transmembrane proteins that are important players in membrane biochemistry and cellular biology [88]. Glycophorins are abundant glycosylated proteins that cover the surface of mature human red blood cells and constitute a receptor for *P. falciparum* ligands. There have been five glycophorins described to date, and three of these

(A, B, and E), underlie the MNS blood grouping system (GYPA, GYPB, and GYPE) [89,90]. The loci encoding glycophorins A, B and E (which is a duplicated gene) are tandem arrays that span a total of 300 kb on chromosomal region 4q31-34. These three genes are highly similar to each other at the nucleotide level (>95%), resulting in unequal recombination and gene conversion [91]. Glycophorin proteins serve as receptors for *P. falciparum* invasion of red blood cells [92]. The parasite genome encodes different functionally interchangeable invasion ligands including EBL-140, EBL1, and EBA-175, which bind to glycophorin C, B, and A, respectively. Although glycophorin A and B are well-known receptors for *P. falciparum* [69] and have higher-than-expected rates of nonsynonymous amino acid substitutions [91], epidemiological data linking specific mutations to resistance to severe malaria were missing until recently.

A recent study of host genetic determinants of severe malaria risk identified a single nucleotide variant in linkage disequilibrium with a complex structural variant at the glycophorin locus that was associated with protection from severe malaria [92]. Leffler demonstrated that a genetic rearrangement of the genes encoding for glycophorins A and B and that also encodes the Dantu blood group antigen confers 40% reduced risk of severe malaria [92]. More recently, Dantu blood antigen has been found to mediate reduced risk for severe malaria through increased surface tension of red blood cells, which prevents parasite invasion [92]. A similar phenotype is observed with ovalocytosis, another hereditary red blood cell disorder that yields rigid, elliptical erythrocytes that have been shown to be resistant to invasion by certain *Plasmodium* [93].

3.3. Enzymopathies

The most common and well-described enzymopathy that has been found to confer some protections to malaria is the Glucose-6-phosphate dehydrogenase (G6PD) deficiency. In this paper, we are reviewing the only G6PD deficiency enzymopathy.

– **GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY.**

Glucose-6-phosphate dehydrogenase is an important enzyme that catalyzes the first reaction in the pentose phosphate pathway of glycolysis [94]. In the erythrocyte, G6PD is the sole enzyme that protects from the buildup of super-radicals and oxidative stress [95]. G6PD deficiency is the most common enzymopathy affecting more than 400 million people worldwide [43] with a global prevalence of 4.9% and a substantial variation among populations [18,37,94,96,97]. The highest prevalence rates, with gene frequencies ranging from of 5 to 25%, are found in tropical Africa, the Middle East, tropical and sub-tropical Asia, some parts of the Mediterranean, and in Papua New Guinea [98]. The G6PD deficiency is less frequent in the Americas (3.4%), Europe (3.9%), and the Pacific (2.9%) as compared to sub-Saharan Africa (7.5%), the Middle East (6.0%), and Asia (4.7%) [97].

Genetically, the G6PD deficiency is an X-linked disorder that is caused by a reduction in the number of enzyme molecules or a structural change causing enzyme instability [94]. The gene that encodes G6PD is 18 kb long, located in a cluster of genes on the distal long arm of the X chromosome (locus q28). The *G6PD* gene is one of the most polymorphic loci in the human genome, with approximately 140 different molecular variants having been identified [94], and contains 13 exons and 12 introns, the length of which varies between 12 bp and 236 bp [99].

The geographical distribution of G6PD deficiency and its high prevalence in areas that are holo-endemic for malaria suggested that it might be protective against *P. falciparum* malaria [91]. However, this hypothesis has been difficult to substantiate via comparison of parasitemia rates and densities between G6PD-deficient males and normal males [43]. Two SNPs, rs1050828 and rs1050829, in the *G6PD* gene have been found to be associated with severe malaria and respiratory distress [100]. The primary form of G6PD enzyme deficiency in Africa is encoded by the derived allele at rs1050828, commonly known as G6PD+202T [101]. Similar but weaker associations have been observed for rs1050829, which marks the ancestral lineage on which G6PD+202 originated [101]. A recent large study demonstrated that G6PD polymorphism had opposite effects on cerebral malaria

and severe malarial anemia phenotypes [21,102,103]. Although the protective mechanism of G6PD deficiency in malaria is not definitive, findings suggest that the protection is related to the susceptibility of G6PD-deficient erythrocytes to oxidative stress [104], which impaired the growth of parasites in G6PD-deficient erythrocytes.

3.4. Immunogenetic Factors

Immunological factors are main components of human body defenses against infectious agents and are classified into two main groups: innate immune system and acquired immune system.

In malaria and most infectious diseases, the innate immune system is the first line defense against infections pathogens and act by controlling parasite growth and regulating the development of adaptive immunity [105]. Because pathogens have tremendous opportunities through mutation to evolve strategies that evade the innate immune defenses, our body obviously develops an adaptive and specific defense mechanism system known as acquired immunity. This specific acquired immunity is regulated by immunogenetic factors. Genetic variability in host immune response genes may account for differences in susceptibility to malaria between groups such as ethnic groups [106]. The immune response induced in humans by infection caused by malaria parasites is complex and varies depending on the level of endemicity, epidemiological factors, genetic makeup, host age, parasite stage and parasite species. Repeated infection and continuous exposure are required to achieve clinical immunity, which reduces the risk of death from malaria and reduces the intensity of clinical symptoms.

Genes of the major histocompatibility complex (MHC) that encode the human leucocyte antigens (HLA) are the most polymorphic known in man [107]. As HLA genes have been evolving over millions of years [108,109], most of the current alleles should have been lost due to genetic drift unless some form of balancing selection was operating [110] without a predominance of any single allele.

3.5. Host Immunogenetic Polymorphisms

Genetic factors play a key role in the susceptibility, progression, and outcome of infectious diseases [111] and there is growing evidence linking these to vulnerability to malaria [55]. In West African children, class I and II human leucocyte antigen (HLA) were found to be independently associated with protection from severe malaria [112]. T-lymphocyte-dependent mechanisms are important in providing protective immunity HLA-B, a polymorphic gene that encodes an MHC class I heavy chain [113,114]. Additionally, a polymorphism in HLA (6p21.3) was found to affect immunological protection against severe malaria [112]. In The Gambia, Hill demonstrated that some polymorphisms, an HLA class I antigen, HLA-Bw53, and an HLA class II haplotype DRB1*1302- DQB1*0501, were associated with reduced susceptibility to severe malaria. Although both HLA-A24 and HLA-B14 of HLA I were more common among the case of severe malaria, their frequencies were statistically significantly low [112]. However, the most common antigen in this Gambian population, the HLA-Bw53, is found to be significantly reduced among cases of severe malaria as compared to mild malaria or the healthy adults [112]. A genetic screening of a small Cameroonian population highlighted the roles of five chromosomal regions containing immune genes influencing the susceptibility to malaria [115,116]. Apinjoh et al. [117] provided evidence that polymorphisms in IL17 may be associated with uncomplicated malaria in the Cameroonian population, while SNPs in IL10, IL17RD, IRF1, TLR1and TLR9 may be linked with severe malaria in general. Polymorphisms in the promoter of coding region(s) of cytokine genes [118,119] may be critical in the development and clinical course of malaria. However, there was a weak association of polymorphism of TLR9 with severe malaria in Malawi and The Gambia [120]. The concentrations of various cytokines increase during malaria, and a high level of circulating TNF-α has been associated with severe malaria [8,121]. Although TNFα is unquestionably an important mediator of malaria immunity and pathogenesis, it remains possible that the observed genetic associations with TNFα

polymorphisms arise from functional variation in neighboring genes [8,122] rather than TNF itself. These factors play an important role in the protection against clinical malaria. Genetic polymorphisms of innate immune system and erythrocytes have been proposed as factors protecting against severe malaria [27,112,123].

The human leukocyte antigen (HLA) complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders [124].

Immunogenetic factors underlying resistance against malaria have been thoroughly investigated [54] and were found to be complex, and mostly adaptive [125]. However, HLA variants protective properties for malaria appear to be local and not universal [126].

In general, the innate response is more important in early childhood survival from malaria, whereas adaptive immune response is more important in older children and adults [127].

Several genetic or genomic studies on susceptibility to malaria have been undertaken; however, the results obtained were conflicting in some cases, due to differences in studied populations [84]. In fact, the HLA polymorphisms, common in West Africans but rare in other races were found to be associated with protection from severe malaria. In addition, HLA class I antigen (HLA Bw53) and HLA class II haplotype (DRB1* 13OZ-DQB1*0501) have been independently associated with protection against severe malaria [128] depending on the genetic constitution of the parasite.

Other determinants of immunological factors such as age and ethnicity were found to influence the manifestations of malaria in Africa. In fact, the ethnic groups in Africa, such as the Fulani, were found to be more protected against malaria infection, suggesting that the risk to malaria may involve the regulation of humoral immune responses [12,129–132]. The low risk to malaria of this ethnic group implied factors probably involved in the regulation of quantitative and/or qualitative antibody response already suggested by the higher humoral responses to *P. falciparum* sporozoite (CSP, TRAP) and blood-stage antigens (MSA-1, Pf-155 RESA, Pf-332) [12]. Although the mechanisms conferring enhanced protection against malaria in the Fulani have yet to be precisely determined, prior studies show that the Fulani tend to have higher levels of *P. falciparum*-specific immunoglobulin (IgM) [133]. Arama et al. [134] demonstrated that the higher immune response in the Fulani and their protection from clinical malaria could derive from a functional deficit of T-regulatory cells. It has also been found in the Fulani ethnic group that the *–590*T allele of the interleukin-4 promoter was associated with elevated levels of anti-malaria antibodies [135]. We can also speculate that the cultural differences, in particular the nomadism and the lifestyle of Fulani living closer to their animals, may make them less exposed to malaria vectors, while another approach supports the contribution of smell, as influenced by the dietary tendencies, to the reduced exposure of Fulani to the vectors.

Both cellular and humoral responses are essential to determine the outcome of the initial infection by malaria parasites, while adaptive immune responses are critically dependent on α/β $CD4^+$ lymphocytes [136]. The concentrations of various cytokines increase during clinical malaria, while a high levels of circulating factors such as TNF-α have been associated with severe malaria [8,121]. Interleukine-12 (IL-12) appears to be critically essential throughout IFN-production by enabling an early and sustained Th1 response [136]. Polymorphism of interleukin-3 gene on chromosomal region 5q31-q33 at SNP *rs40401* was found to be associated with a protective effect against malaria attacks in both population- and family-based analyses [137]. Another candidate gene study indicated that polymorphisms of both TLR1 and TLR6 were significantly associated with mild malaria in a population from Brazil [138]. Recently, from a case–control study, Domingues [139] suggested an association of IL10 polymorphism (-3575 T/A) with malaria symptoms.

In summary, immunogenetic factors explain the genetic basis of the immune reaction to disease.

4. Conclusions

Plasmodia have been an adaptive selection force of the human genome during their co-evolution. There is no unique genetic factor of susceptibility or resistance to malaria in endemic areas despite some well-known and universally accepted genetic factors already described. Resistance to malaria

appears to be heterogenic and multifactorial; therefore, the role of genetic and non-genetic factors need to be investigated in low-incidence as well as high-incidence populations in order to improve our understanding of their contribution to susceptibility to the disease.

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